



EFFICACY OF PLASMA EXCHANGE IN TREATMENT OF ACUTE AUTOIMMUNE NEUROPATHY (GUILLIAN BARRE SYNDROME)

Nephrology

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ABSTRACT

Background And Aim: Plasmapheresis or plasma exchange is the most effective and treatment of choice in many neurological disorders. Thus the objective was to study the efficacy of plasmapheresis, compared to other therapies in acute autoimmune neurological disorders. **Materials And Methods:** A prospective interventional study done on 164 patients with acute neurological disorder i.e., GuillainBarre Syndrome (GBS) admitted in a tertiary hospital in South India. 22 patients were treated with IVIg, 46 with small volume plasma exchange (SmVPE) and 5 with large volume plasma exchange (LVPE). They were compared with 91 patients on supportive therapy. Outcome of treatment was assessed by Hughes disability score and mortality at the end of 2 weeks, one month and 3 months. Data analysed in percentages, paired and unpaired t-test. **Results:** Out of 164 patients, 1.8% overall mortality and 13.6% mortality in IVIg treated patients alone was observed. Although early recovery (14 days) was seen with IVIg compared to plasmapheresis (18 days), improve in muscle weakness was more by one grade early in SmVPE than IVIg. Statistically significant improvement was seen in three treatment modalities compared to control but equal efficacy observed in plasma exchange and IVIg. **Conclusions:** In a developing country like India where socio economic status is very low where many people who can't afford costlier treatment like IVIG and PE, they can be treated with small volume plasma exchanges which are cheaper and with fewer complications.

KEYWORDS

Acute neurological disorder, Efficacy, Plasma exchange.

INTRODUCTION

Plasma exchange (PE) was introduced as a possible treatment in 1978 and was shown to offer significant benefit by a randomized trial published in 1985 [1, 2]. Plasma exchange (PE) involves the separation and removal of plasma from corpuscular blood and the replacement of it with various fluids, while plasmapheresis only refers to the removal of plasma by extracorporeal blood purification methods. Most neurological disorders that are treated with PE are associated with presumed aberrant humoral immune responses, including myasthenia gravis, Guillain-Barré syndrome (GBS), and chronic inflammatory demyelinating polyneuropathy (CIPD) [3]. Guillain-Barre syndrome (GBS) is an immune-mediated disorder of nervous system of acute or subacute onset characterized commonly by generalized progressive weakness of arms and legs, limb paraesthesias and relative or complete areflexia [4,5]. GBS (acute autoimmune neuropathy) constitutes a serious emergency as it is the most frequent cause of acute flaccid paralysis in India. The world-wide incidence of this disease is about the incidence was 1.3 per 100,000 person-years [6]. The prognosis of GBS is usually good, showing a complete functional recovery or with minimal deficits in the 90% of patients 1 year after the onset of illness [7]. Death rate is described to be between 2.15% to 5.4% (8). Intravenous immunoglobulin (IVIg) and plasma exchange are the cornerstones of treatment since decades. But despite these treatments, 25% initially progress in muscle weakness, 25% require artificial ventilation, 20% is still not able to walk independently after 6 months, and 2–5% die, emphasizing the need for better treatment [9]. It became the gold standard against other treatments as it hastens recovery [10]. But it is expensive and requires the help of trained personnel therefore unsuitable for many centres in developing countries. Intravenous immunoglobulin (IVIg) was introduced for GBS in 1988 [11]. In 1992, the first randomized trial comparing IVIg and PE showed similar effects from each treatment [12]. Manual small volume plasma exchanges appears to be economical, technically simpler procedure, with relatively minor and fewer complications. With small volume plasma exchanges the onset of recovery will be early, progression can be slowed and thereby we can reduce the disability. However, the data regarding clinicoepidemiological profile and outcome of the patients with GBS on plasma exchange from developing countries like India are very limited. The present study evaluate the efficacy of plasmapheresis or small volume plasma exchanges in GBS patients and assess their therapeutic outcomes after 2 weeks, 1 month and 3 months.

MATERIAL AND METHODS

This prospective interventional study was done by Department of

Nephrology, in the tertiary hospital in South India to evaluate the efficacy of plasmapheresis on patients with non-renal indication. Total of 164 patients who were diagnosed of Guillain Barre Syndrome (acute autoimmune neuropathy) fulfilling the Cornblath criteria as modified by Asbury were taken from the pool of inpatients from various medical wards and Neurology ward. Institutional Ethics Committee approved the study protocol and written informed consent was taken from all relatives of participant. Out of them 22 patients were treated with IVIG, 46 patients were treated with SmVPE, 5 patients were treated with large volume PE, and 91 patients were treated with supportive therapy randomly depending on the availability, acceptability, affordability of treatment modalities.

Patients who were given supportive therapy were taken as control group to compare with treatment group. All patients were evaluated with clinical history and detailed neurological examination at admission daily during inpatient stay and at 2 weeks, 1 month, 3 months after discharge. Baseline investigations, biochemical investigations including blood sugar, renal parameters, serum electrolytes, HIV, HBSAg were done in all patients. Nerve conduction studies using a Nicolet Viasys machine were done. Special investigations like anti ganglioside antibodies is an expensive test which were done outside and done for people who can afford it. Patients were admitted in critical care neurology ward which is well equipped with centralized oxygen, continuous multi-channel monitoring and good nursing care. All patients requiring ventilator support are managed in the respiratory intensive care unit. The patients are treated with I.V Immunoglobulins for those patients who can afford it. Plasmapheresis or small volume plasma exchanges were done in our blood bank. The outcome at 2 weeks, 1 month and 3 months is assessed. The disability and weakness are determined by GBS disability score (Hughes grading) and MRC sum score. GBS disability scale (Hughes grading) [13].

0. Healthy

1. Minor symptoms or signs of neuropathy but capable of manual work/capable of running
 2. Able to walk without support of a stick (5m across an open space) but incapable of manual work/running
 3. Able to walk with a stick, appliance or support (5m across an open space)
 4. Confined to bed or chair bound
 5. Requiring assisted ventilation (for any part of the day or night)
 6. Death
- Technique of immunoglobulins (IVIG)

Total of 2 gm/kg body wt of IVIG (0.4 gm of IVIg/kg of body weight was administered on 5 consecutive days) was infused over 5 days continuously using infusion pumps in the neurology critical care unit.(14)

Technique of Large volume plasma exchange (14) :

Continuous flow machines were used. They remove whole blood from one intravenous site while simultaneously and continuously returning the reconstituted elements through another intravenous site. They shorten the time of PP. We removed 40 ml/kg of plasma. This was replaced with albumin or FFP in combination with sterile saline. Citrate is usually used for anticoagulation. The entire procedure was done using dialysis machines.

Technique of small volume plasma exchange [15, 16].

1. Collection of blood: blood is collected by the usual venesection and phlebotomy, from the antecubital vein as used for blood donation. A double blood bag system is used and about 350ml blood is collected per session.

2. Separation of plasma: Double-blood bag is centrifuged in a refrigerated centrifuge at a speed of 1500-2500G (fast spin) for 10 minutes. The double blood bag is kept in a plasma extractor, which separates out the plasma in one bag while the packed cells are left behind the original bag.

3. Transfusion of packed cells: Bag with plasma is discarded in blood bank and the bag with packed red cells is sent to ward, where it is transfused back into the patient.

4. Transfusion of plasma: After every two sessions of manual plasmapheresis, the patient is transfused about 200ml of plasma to make up for the lost plasma. About 200 ml of plasma is thus removed per session of manual plasmapheresis. An individual patient may require 10-15 sessions for treatment. Around 50 ml of plasma per kg body weight was removed.

Efficacy of treatment was measured by primary and secondary outcomes. Primary outcome measured by mortality(respiratory failure). Secondary outcome assessed by improvement in functional ability i.e., ability to walk with support and without support. Data from the proforma were filled into MS Excel 2010 and analyzed by SPSS 23 version. For descriptive analysis frequency, percentage, mean, median, standard deviation were calculated and presented in tabular form whereas for inferential statistics independent t-test, paired t test was applied as per need to find out the difference between groups. We consider values as statistically significant at a 95% confidence interval if $p < 0.05$.

RESULTS

This prospective study was planned to assess the efficacy of different treatment modalities in 164 patients with Guillain Barre syndrome.

Clinical Course

Different treatment modalities adopted for treating GBS patients were given in Fig. 1. Out of 164 patients intravenous immunoglobulin (IVIg - 0.4 mg/kg/day) was given in 22 patients (13.4%), large volume PE was given in 5 (3%) patients, small volume PE was given in 46 (28.1%) patients and physiotherapy was alone given in 91 (55.5%) patients. Their outcome was measured at 2 weeks, 1 month, and 3 months.

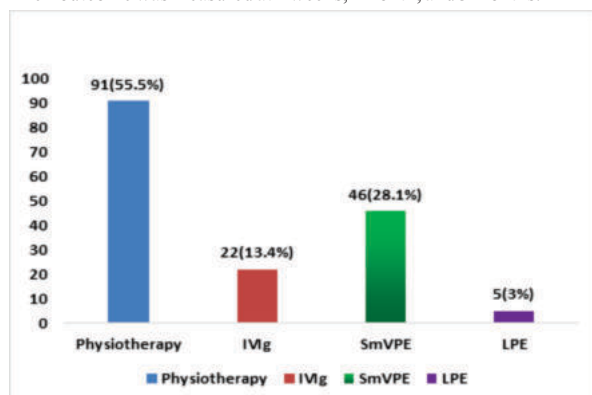


Figure 1. Treatment Modalities.

Results in SmVPE

There were 21 patients in grade 4, 21 patients in grade 3, 3 patients in grade 2 and 1 patient in grade 1 at entry in SmVPE. Age range was 13 to 75 years. The median age of SmVPE study group was 30.5 years and of the control group was 33.53 years. In PT group 1 patient in grade 5, 52 patients in grade 4, 29 patients in grade 3 and 9 patients in grade 2. The median time in days to reach to grade 4 was 7 days in SmVPE group and control group. As soon as patients were admitted and willing for treatment SmVPE started. The progression of disease was arrested and recovery started earlier in SmVPE group and they took shorter time to improve by one clinical grade ($p < 0.001$, highly significant). They also attained better clinical grades on the disability scale at the end of 2 weeks, first and three months ($p < 0.001$, highly significant). The treatment failure rate, defined as failure to improve by a minimum of one grade at the end of 3 months, was also significantly lower in the SmVPE group ($p < 0.001$). (Table 1).

Table 1. Comparison Of Outcome Of Small Volume PE And Control Group.

GBS score	At onset		At discharge		At 2wks		At 1 Month		At 3 Months	
	SmV PE (46)	PT (91)	SmV PE*	PT	SmV PE*	PT	SmV PE*	PT	SmV PE*	PT
1	1(2.2)	0	1	0	1	0	1	0	4(8.7)	16(17.6)
2	3(6.6)	9(10)	13	13	15	13	26	17	31(67.4)	22(24.2)
3	21(45.6)	29(31.8)	28	31	27	34	16	38	10(21.7)	23(25.2)
4	21(45.6)	52(57.1)	4	47	3	44	3	36	1(2.2)	30(33)
5	0	1(1.1)	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0

*Paired t test < 0.001

Patients with score 4 were not willing for treatment as they have relatively good muscle power and does not want to give consent for treatment.

Secondary Outcomes- Comparison Between Different Treatment Modalities

Secondary outcome assessed by the time taken to walk with aid, without aid and recovery from bedridden state. Table 2,3,4 has given comparison between different treatment modalities in the improvement of the disease with time. Patients on Large volume plasma exchange (LvPE - 40%) have improved more by 2 weeks compared to others. IVIg and SmVPE have improved by one month better than PT. (Table 2) Time taken to walk unaided was early in LvPE and IVIg and next in SmVPE the end of 3 months patients on IVIg showed more improvement. Very less improvement was seen in supportive therapy patients. (Table 3) No patients improved from bedridden stage in LVPE received patient. Hughes grading in IVIg group was grade 1 -1 patient, grade 3 -3 patients, grade 4 -16 patients, grade 5 -2 patients. Hughes grading in LVPE group was grade 3 -2 patients, grade 4 -3 patients. Early recovery from bedridden to walking with support was seen in SmVPE than other treatment modalities. (Table 4) One patient remained in bed ridden state at the end of 3 months in patient on Large volume plasma exchange. Out of 164 patients, 3 patients on IVIg died at the time of discharge with reasons unknown. Thus mortality rate in our study with GBS was 1.8%. Patients died because of respiratory failure.

Table 2. Secondary Outcome: Time Taken To Walk With Aid

Treatment group	At discharge No. of patients	2 weeks	1 month	3 months
PT	31(34%)	31(34%)	27(29.7%)	23(25.3%)
SmVPE	28(60.9%)	27(58.7%)	20(43.5%)	10(21.7%)
IVIg	8(36.4%)	7(31.8%)	6(21.3%)	2(9%)
LV PE	4(80%)	2(40%)	1(20%)	1(20%)
Total	71(43.3%)	67(40.8%)	54(33%)	35(21.3%)

Table 3. Secondary Outcome: Time Taken To Walk Without Aid.

Treatment Group	At Discharge	2 weeks	1 month	3 months
PT	13(14.3%)	13(14.3%)	17(18.7%)	22(24.2%)

SmVPE	13(28%)	15(32.6%)	22(47.8%)	31(67.4%)
IVIg	3(13.6%)	5(22.7%)	10(47.6%)	16(72.7%)
LV PE	0	2(40%)	3(60%)	2(40%)
Total	29(17.7%)	35(21.3%)	52(31.7%)	71(43.3%)

Treatment not willing patients were given physiotherapy. LVPE Patients died because of their severity and complications.

Table 4. Secondary Outcome: Bedridden.

Treatment group	At admission	At discharge	2 weeks	1 month	3 months
PT(91)	52(57.1%)	46(50.5%)	43(47.2%)	35(38.5%)	30(33%)
SmVPE (46)	21(45.6%)	04(8.7%)	03(6.5%)	03(6.5%)	01(2.2%)
IVIg(22)	12(54.5%)	07(31.8%)	07(31.8%)	03(13.6%)	01(4.5%)
LVPE(5)	3(60%)	01(20%)	01(20%)	01(20%)	01(20%)
Total (164)	88(53.6%)	58(35.4%)	54(32.9%)	42(25.6%)	33(20.1%)

The average duration of illness before treatment in IVIG group was 7.6 days and in control it was 11.6 days. Small volume plasma exchange was started within median days of 11.67 days. The onset of recovery started in 14 days in IVIG group where as it was 24 days in control group and 18 days in SmVPE. Total of 40-50 ml /kg body weight of plasma was exchanged over a period of 10-12 days. No major complications were developed during the procedure necessitating its termination. Ten patients developed urticaria after transfusion of fresh frozen plasma which improved with anti-histamines. No other complications were noted. (Fig 2) Early improvement was seen in SmVPE compared to control group.

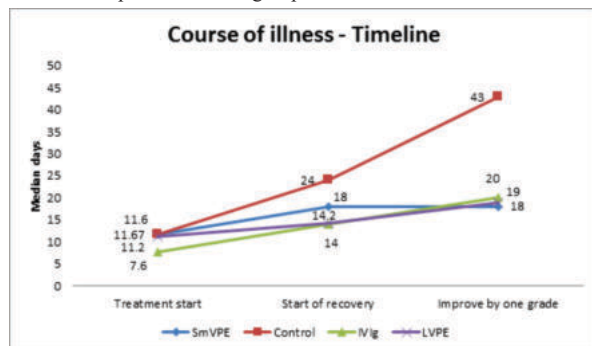


Figure 2. Time line Of Course Of Illness In SmVPE And Control Group.

Mean GBS score at admission were PT-3.49 $\pm$ 0.69, IVIg - 3.91 $\pm$ 0.92, SmVPE-3.35 $\pm$ 0.71, LVPE - 3.4 $\pm$ 0.89. By the end of follow up, all the treatment modalities shown statistically significant improvement with time. Compared to supportive therapy all other treatment modalities like SmVPE, IVIg, LVPE shown statistically significant improvement. Comparatively more mean improvement in grades was seen in IVIg received patients. (Table 5) But there was no statistically significant difference in outcome of IVIg and plasmapheresis.

Table 5. Comparison Of Hughes GBS Score In Treatment Groups At The End Of Study.

Treatment	Mean GBS score At admission	Mean GBS score After 3 months	Paired t test	Improvement	T-test Vs Control
PT	3.49 $\pm$ 0.69	3.08 $\pm$ 0.81	<0.0001*	0.42 $\pm$ 0.5	
IVIg	3.91 $\pm$ 0.92	2.5 $\pm$ 1.6	<0.0001*	1.41 $\pm$ 1.1	<0.0001*
SmVPE	3.35 $\pm$ 0.71	2.17 $\pm$ 0.61	<0.0001*	1.17 $\pm$ 0.49	<0.0001*
LPE	3.4 $\pm$ 0.89	2.4 $\pm$ 1.14	0.03*	1.0 $\pm$ 0.71	0.014*

DISCUSSION

This study was aimed to assess the efficacy of IVIG, large volume PE, small volume PE in GBS affected patients through a prospective hospital based data. The data was separately analysed for different treatment modalities in GBS patients and their therapeutic outcome at 2 weeks, one month, and 3 months. This data was compared with control group. 1.8% mortality rate was observed at the end of our study, 0.6% with no improvement (Bedridden) and 97.5% overall improvement. Out of the patients died, all were on IVIg treatment

(13.63%) and no deaths in patients on plasma exchange. This may be because of selection bias for doing small volume plasma exchanges in patients who were not progressing faster and those who were not on ventilator or impending respiratory failure. As per Dhadke et al. in a study done in Solapur, 21.5% patients on IVIg died while all on plasmapheresis survived [17]. The mortality in the study done by Rangan et al. [18] on Pediatric age group was 6.6% whereas the mortality rate in study by Kalra et al. [19] was as high as 11% and that by Nasiri et al. [20] was the lowest at 1.8%. The improvement in Hughes score was little more in patients on IVIg followed by plasmapheresis but statistically significant difference in improvement was not seen. IVIg and plasma exchange treatment were effective compared to control and statistically significant as proven by other studies [9]. Patel et al. in a study in tertiary care centre in Ahmedabad showed that the improvement in Hughes Score on discharge was 0.64 $\pm$ 0.23 in patients treated with Plasmapheresis (n=25) compared to a 0.69 $\pm$ 0.04 improvement in score in patients treated with IVIG (n=16) and did not significantly differ in short-term functional outcomes regarding improvement in Hughes Score (p=0.89) [21]. As per many randomised trials there was equal efficacy between IVIg and plasmapheresis [12, 21, 22]. Our study has also shown that both the treatment modalities were effective but statistically significant advantage over the other was not observed. However Kishore et al. in their study done to assess the efficacy of both treatments found that plasmapheresis was associated with more improvement in comparison to IVIg [23]. The onset of recovery was faster in patients on IVIg followed by Plasmapheresis and control in our study. Although IVIg and PE are probably of equal efficacy, faster recovery have been observed with IVIg in trials designed to compare it to PE [17, 21]. The primary outcome like improvement in muscle weakness using Hughes grading was more in IVIG group compared to control group at 2 weeks, one month, and 3 months after discharge (p<0.001- highly significant). One would have expected a poor prognosis, but the SmVPE patients recovered from weakness significantly better than control group in many aspects. Supporting our finding, Sudhir Kumar from CMC Vellore and Tharakan et al. from Sree Chitra Tirunal Institute, Trivendrum have successfully used the method of manual plasmapheresis (low volume) in a large number of patients. They noted a faster clinical recovery and fewer complications in the plasmapheresis treated group compared to the controls [15, 16]. Along with efficacy, cost-effectiveness is an important factor for treatment choice, especially in developing countries. In developing countries, using small volumes of Plasma exchange may bring down the cost when compared to IVIG. The main limitations for the use of Plasma exchange would be the availability of technical expertise and support [24].

Limitations of this study was the time duration for follow up was less as we have taken 3 months as the end point for follow up. Long term follow up until one year may give a better picture of morbidity of the patients. Study group was also small and we cannot generalize it. As this study included only in-hospital subjects, this may not reflect true incidence of disease in the community. There might be slight under reporting of older people. Strength of this study was it was a prospective one where follow up was done for 3 months. Most of the investigations needed to diagnose GBS were done in the hospital. So there was no delay in diagnosis and treatment was started without any delay. SmVPE was done without any financial burden to patient. It was provided free of cost to the patient by hospital. It is among the few studies in the country to deliver data regarding the clinical-epidemiological profile and outcome of the GBS. Further studies with large sample size and long term follow up needed to assess the progress of disease. The prospective studies emphasizing the predictors of favourable outcome may enlighten about the better prognostic determinants of GBS. More studies to clarify the efficacy of newer modalities of treatment are needed especially in Asian population.

CONCLUSION

Improvement in muscle weakness was significantly good in IVIG group, PE group and SmVPE group compared to control group at 2 weeks, one month, and 3 months after discharge. Small volume PE accelerates the recovery earlier and arrests progression of disease earlier. Complications and disability were less compared to large volume PE. Plasmapheresis (LVPE) is expensive and requires the help of trained personnel and therefore, is unsuitable for many centres in developing countries. Comparatively Manual small volume plasma exchanges appears to be economical, technically simpler procedure, with relatively minor and fewer complications.

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